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January 9, 2004
Date

Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Spies et al.

Serial No.: 09/855,612

Filed: May 14, 2001

For: Cell Stress Regulated Human MHC Class I Gene

Group Art Unit: 1644

Examiner: Vandervegt, Francois P.

Atty. Dkt. No.: FHCC:003USC1

RESPONSE TO OFFICE ACTION DATED SEPTEMBER 9, 2003

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper is submitted in response to the Office Action dated September 9, 2003 for which the three-month date for response was December 9, 2003.

A request for a one-month extension of time to respond is included herewith along with the required fee. This one-month extension will bring the due date to January 9, 2004, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/FHCC:003USC1.

Reconsideration of the application is respectfully requested.

RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-25 were pending prior to the Office Action dated September 9, 2003 ("Action").

B. Clarification of Statement Made in Earlier Response

In the previous Office Action, dated March 11, 2003 ("March Office Action"), the claims were rejected as lacking enablement. The examiner argued that "it is not clear that the expression of MICA in two endothelial cell lines is indicative of the expression of MICA or MICB in actual endothelial cancers ...."

Applicants filed a response to the March Office Action on June 11, 2003 ("June Response"). In that response, Applicants argued that the specification showed the presence of MICA and MICB in two types of cancer cell lines, astrocytomas and colon carcinomas. Applicants further provided evidence that articles published subsequent to the filing date of the application supported the present claims. In addition to citing Takehara *et al.* (2003) (citation should have been to Jinushi *et al.*) and Groh *et al.* (1990), Applicants stated, "The presence of MICA and MICB in astrocytoma and colon carcinoma cell lines, as supported by page 75, lines 6-9 and page 76, lines 24-25, which clearly show that MICA and MICB are associated with a wide variety of cancers." June Response at page 4. Applicants then contended, "Thus, just as the present application alleges, and the present claims recite, MICA and MICA can be used to identify many different tumors, and only routine experimentation is required to employ this invention." *Id.*

Applicants submit herewith a declaration from the inventors, Drs. Thomas Spies and Veronika Groh ("Declaration"), to clarify a statement made in the June Response.[1] The Declaration states that the inventors are of the opinion "that expression of MICA and MICB in tumor cell lines is not necessarily indicative of cancer because MICA and MICB expression is frequently induced in rapidly proliferating cell lines commonly used in a laboratory." Declaration at ¶ 3.

The Declaration also says, "Nonetheless, the observation of expression of MICA and MICB in freshly isolated tumor cell suspensions, as discussed in the paper of Groh *et al.*, (1999), was indicative of cancer. Such evidence is also relied on by the argument offered in the Response, which cites the Groh *et al.* paper. This reference reports that freshly isolated tumor specimens from carcinomas of the lung, breast, kidney, ovary, prostate and colon express MICA and MICB. As stated in the Response, this evidence supports the claimed invention." Declaration at ¶ 4.

C. Claims 1-25 Are Enabled

The Action rejects claims 1-25 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. More specifically, the Action contends that because the art teaches that normal cells or stressed cells express MICA/B, then the skilled artisan would not have been able to predict that the mere detection of MICA/B in sample was indicative of cancer, and therefore, would need to know how to correlate the expression levels of MICA/B with the presence of cancer. The Action relies on the references of Groh *et al.*, *Proc. Natl. Acad.*

[1] The Declaration was executed on July 28, 2003, after it was identified that a statement in the June Response required clarification. Unfortunately, due to an extended leave of absence by Applicants' representative, the Declaration was not promptly filed. Only after the present Office Action was received did Applicants' representative appreciate that the executed Declaration was not filed, and is being submitted herewith.

Sci., 12445-12450, 1996 ("Groh 1996 reference") and Groh *et al.*, Science 279:1737-1740, 1998 ("Groh 1998 reference). Applicants respectfully traverse this rejection.

As discussed in the previous section and as stated in the inventors' Declaration, the detection of expression of MICA and MICB in rapidly proliferating cell lines is not indicative of cancer because such cell lines have been observed to express MICA and MICB. The Action cites to references—the Groh 1996 reference and the Groh 1998 reference—that used cell lines in their studies. The skilled artisan would understand then that these references are of limited relevance to the claimed method. The claimed method involves detecting a cancer cell in a sample, and it would be expected that the sample would not include cells from a cell line. Thus, the skilled artisan will predict that detection of MICA or MICB in the sample could be indicative of cancer, as opposed to expression from normal cells. Furthermore, that skilled person would also know that there are other factors that might lead one to suspect that a particular patient from whom the sample was obtained had cancer.

The specification further supports the claimed invention, as on page 7, lines 5-6, which states that "[t]he present inventors have determined that MICA and MICB are ***expressed at the cell surface*** of colon and other cancer cells." Emphasis added.

Moreover, there is other evidence to support the application. In a 1999 reference, the observation of expression of MICA and MICB in **freshly isolated tumor cell suspensions** (in contrast to cell lines) from lung, breast, kidney, ovary, prostate and colon was indicative of cancer (Groh *et al.*, *Proc. Natl. Acad. Sci.*, 96:6879-6884, 1999, attached with June Response). The Declaration asserts this much. It states that "the observation of expression of MICA and MICB in freshly isolated tumor cell suspensions, as discussed in the paper of Groh *et al.*, (1999), was indicative of cancer." Declaration at ¶4. Also, Jinushi *et al.* (2003) show expression of

MICA and MICB in hepatocellular carcinoma tissue express MICA and MICB. (Jinushi *et al.*, *Int. J. Cancer*, 104: 354-361, 2003, attached with June Response).

Thus, just as the present application alleges, and the present claims recite, MICA and MICB can be used to identify many different tumors, and only routine experimentation is required to employ this invention. Therefore, applicants respectfully submit that sufficient rebuttal evidence has been provided to establish that MICA and MICB can, in fact, be used as the basis for cancer identification.

D. Claims 1-25 Are Definite

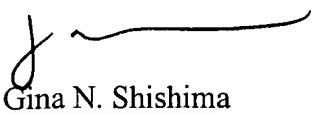
The Action contends that the claims are indefinite because a step is omitted from the claimed method. The omitted step is alleged to be a step for correlating expression levels of MICA and/or MICB with cancer. In light of the discussion above, Applicants submit that no correlation step is required. Consequently, the claims are not indefinite, and Applicants respectfully request this rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



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Date: January 9, 2004